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RESEARCH perspectives

Clinical Implications of the Latest Data on Metastatic Melanoma

CME Activity

Overview

Kim Margolin, MD, analyzes 4 key studies in metastatic melanoma, considering the clinical implications and application of several new classes of treatment.

Content Areas

- Treatment selection
- OPTiM trial
- KEYNOTE-001 trial
- Combination treatment

Target Audience

Oncologists, hematologist/oncologists, dermatologists, and other healthcare professionals who care for patients with metastatic melanoma

This activity is supported by educational funding provided by Amgen and Prometheus Laboratories Inc.

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Commentary on 4 articles:

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CE/CME Statement

Target Audience
This activity was developed for oncologists, hematologists/oncologists, dermatologists, and other health care professionals who care for patients with metastatic melanoma.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the treatment of metastatic melanoma
- Incorporate evidence-based research into clinical practice

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1 Overall Survival and Durable Responses in Patients With *BRAF* V600–Mutant Metastatic Melanoma Receiving Dabrafenib Combined with Trametinib

Long GV, et al.

Dr. Kim Margolin

Hello. This is Dr. Kim Margolin, professor in medical oncology at the City of Hope National Medical Center. The first article we will be discussing is entitled Overall Survival and Durable Responses in Patients With *BRAF* V600–Mutant Metastatic Melanoma Receiving Dabrafenib Combined with Trametinib. The summary of this article is as follows: In this episode we're going to discuss the study by Dr. Georgina Long and her colleagues of the clinical correlates of sustained responses and overall survival in patients treated with dabrafenib combined with trametinib. This was a post hoc analysis of 78 patients who received a combination of dabrafenib and trametinib in previously reported phase 1 and phase 2 trials. These patients all received the recommended phase 2 dose of dabrafenib, 150 mg twice a day, and trametinib 2 mg daily (the same doses that were used in subsequent phase 3 trials) and they had not previously been treated with a *BRAF* inhibitor.

The importance of this study is that with the remarkable activity of new molecularly-targeted and immunotherapeutic agents for melanoma and other malignancies, many trials are reported early and require more prolonged follow-up as well as subset analysis to detect patient characteristics associated with favorable outcomes that may be of prognostic and/or predictive value. Such analyses may also be important for identifying risk factors for important treatment toxicities.

In my description of the study, the methods are as follows: The disease and patient characteristics of importance include that the 78 patients in this study, all with activating *BRAF*-mutated advanced melanoma, were treated with dabrafenib 150 mg twice a day and trametinib 2 mg daily. In the *BRAF* inhibitor naïve cohorts from a multi-tiered phase 1 and 2 study. In patient outcomes, 61 patients during the study progressed during treatment, 9 discontinued treatment without evidence of disease progression, and 8 remained on treatment without progression. The median follow-up of this report is 45 months.

The key findings will now be presented. Serum lactate dehydrogenase level, or LDH, was associated with treatment outcomes. Patients with a continued long-term response without progression were more likely to have normal LDH at baseline and prolonged survival was also associated with normal LDH at baseline. In patients with a normal LDH, the median overall survival was 45.5 months compared to 16.6 months in patients with an elevated baseline LDH. After a year, survival was 88% for those patients with normal LDH vs 68% in patients with elevated LDH at baseline.

This trend continued. Sixty-two percent of the patients with normal LDH survived to 3 years compared with only 5% of patients with elevated LDH at baseline. Prolonged survival was associated with a normal LDH at baseline and fewer organ sites of metastatic disease at baseline. Patterns of progression were also reported. When patients progressed, almost two-thirds had new metastases rather than progression of an existing metastatic site. Of these, 75% were treated following progression, either with the same combination as reported here or with another systemic treatment. These included immunotherapy and tumor infiltrating lymphocyte transfer, as well as radiation therapy.

At the time of progression, most patients had metastases; 65% vs 35% progression at existing sites. Of those patients who had progressed, three-quarters went on to receive subsequent systemic therapy that in some cases included continuation of treatment with dabrafenib and trametinib, for example, with or after a local intervention such as radiation therapy or surgery. Of the 15 patients who went on to receive immunotherapy, they had a median survival of 36.5 months from the time of starting study treatment, that is from the beginning of their dabrafenib and trametinib therapy.

Of those patients who continued to receive dabrafenib and trametinib, of whom there were 17 following progression, there was a median overall survival of 25 months. For those who went on to receive immunotherapy, all survived at 1 year, 65% at 2 years and 53% remained alive at 3 years. Those who went on to receive a combination therapy were all alive at 1 year, 53% at 2 years and 29% at 3 years.

My thoughts and analysis of this study are as follows: The main points of the study from my perspective include the fact that initial data for single-agent *BRAF* and also for MEK kinase inhibitors, had shown a high response rate but a short median response duration and progression-free survival in patients with an activating *BRAF*-mutant melanoma.

Combination MAP kinase inhibitors, such as dabrafenib plus trametinib, or vemurafenib plus cobimetinib, enhanced the median response duration and progression-free survival and modestly benefited survival. The emergence of drug resistance in nearly all patients has led to a general sense of nihilism about the benefits of these agents as well as a reluctance to use them in the first-line setting. This report's importance is to highlight that features associated with a favorable prognosis, in general, for melanoma as well as for other cancers, can also be associated with prolonged benefit from the combined MAP kinase inhibitors.

Since these patient factors are not likely the cause of mutations that lead to therapy resistance in the tumor, these observations further support the concept that targeted agents are working in large part through immune response to altered tumor and the tumor microenvironment. These are mechanisms that have been long associated with greater benefits in patients with a lower disease burden and less immunoresistant biology. Those patients include normal LDH, earlier M-stage, and fewer organ sites of disease.

The results of this study impact the current state of patient management by providing additional prognostic information to help both physician and patient to select the first-line therapy and to have more accurate information regarding the expected outcomes of first-line therapy. The future state of patient management may also be affected by the results of this study because they provide new baseline data for patient subsets that will inform the design of clinical trials. But there remain some unanswered questions. For example, the selection of first-line therapy and therapy sequence for the most favorable patient subsets if patients do have an activating *BRAF*-mutant melanoma.

This question will be answered in large part by a new and rapidly accruing study, EA6134, that compares first-line treatment with double immune checkpoint blocking agents vs dabrafenib plus trametinib double MAP kinase inhibitors. Internal crossover within that study will also allow for the observation of the effect of sequencing first- and second-line therapy in these patients. We will also learn the molecular and immunologic factors that may allow for even better patient selection at the outcome.

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Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Andtbacka RHI, et al.

Dr. Kim Margolin

Hello. This is Dr. Kim Margolin, professor in medical oncology at the City of Hope National Medical Center. The article that we will be discussing is entitled Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. The lead study author is Robert Andtbacka. In this episode, we're discussing Dr. Andtbacka et al's report of talimogene laherparepvec, otherwise known as T-VEC, in advanced melanoma. This study was an open-label randomized phase 3 trial where patients with unresectable melanoma that was safely accessible for intralesional injections were treated with direct intratumoral injection of T-VEC, or with subcutaneous GM-CSF. The importance of this study is that T-VEC is the first oncolytic immunotherapy for melanoma that has shown patient benefit. Compared to other immunotherapies, the responses to T-VEC were durable while toxicity was limited.

Lesional immunomodulatory therapy has unique benefits and the potential for important combinations that were launched with this study and the ensuing FDA approval of this agent. I would like to describe the study methods. Patient disease characteristics were based on the fact that this was a study for patients with unresectable stage III or stage IV metastatic melanoma. At least one lesion had to be accessible for intratumoral injection. Serum lactate dehydrogenase, or LDH, had to be less than or equal to 1.5 times the institutional upper limit of normal. Patients must have had an ECOG performance status ≤1, and if liver metastases were present, they must have been stable clinically for at least one month. Patients were excluded if they had bone metastases, untreated brain metastases, >3 visceral metastases, or visceral metastasis over 3 cm in diameter. The trial was an open-label phase 3 design with 436 patients who were randomized 2:1 to receive T-VEC or subcutaneous GM-CSF.

It was a multi-center, open-label phase 3 trial with a 2:1 randomization that led to the accrual of 295 patients to receive T-VEC, and 141 patients randomized to receive GM-CSF. Treatment dosing included the administration of T-VEC during the treatment phase of the trial into some or all of the non-visceral lesions. Both T-VEC and GM-CSF were to be continued for at least 24 weeks unless an alternative treatment was indicated, generally because of progressive disease. Thereafter, most patients went on to protocol-mandated discontinuation of therapy, either because of progressive disease, treatment toxicity, or the achievement of a durable response.

The initial treatment was 106, or one million, plaque-forming units per ml, and subsequently T-VEC at 108, or 100 million plaque-forming units of virus per ml. Administration interval was every 2 weeks at the higher dose after a 3-week pause after the first dose to assess for safety. Some or all of the safely accessible lesions were to be injected at each visit but visceral lesions were not injected.

In the patients who were randomized to receive GM-CSF, it was given subcutaneously at 125μg/m^2 daily for 14 consecutive days of every 28-day treatment cycle. Treatment was also administered for at least 24 weeks unless an alternative treatment was indicated because of progressive disease or toxicity. Therapy was continued until disease progression, either based on a reduced performance status, intolerable adverse events, achievement of complete remission, lack of response after 12 months of treatment, or disappearance of all injectable lesions in the T-VEC arm, making it impossible to inject any further intratumoral injections.

Treatment could be continued for up to 6 months in patients with stable or responding disease. The endpoint of the trial included the durable response rate, which is the combined complete and partial responses lasting at least 6 months. That was the primary endpoint. The overall survival, the timing of onset and duration of response, the time to treatment failure, and a number of other secondary endpoints, including immune responses, were also prespecified in the protocol. The primary endpoint therefore was complete and partial responses lasting at least 6 months and starting within the first 12 months. The median follow-up for the overall survival analysis was 44 months and the median treatment duration for both therapy arms was 23 weeks.

The key findings of the study are now to be reported. For the primary endpoint, T-VEC treatment provided a durable response rate of 16% compared to 2% for GM-CSF, and 65% of the patients in the T-VEC arm of the study continued to be responding after 12 months, whereas this was the case for only 47% of patients treated with GM-CSF who responded to therapy. The time to response for both treatments was that which would be expected for immunotherapies, sometimes delayed. T-VEC responses occurred after median of 4 months and 58% of these responding patients met the criteria for disease progression prior to achieving objective response.

The durable remission rate for T-VEC was 16.3% compared to 2.1% for GM-CSF, and the difference between these values produced a *P*-value of <0.001. The estimated probability of still being responsive, that is a partial or complete response after 12 months, was 65% for 78 responders treated with T-VEC compared to 47% among the 8 responders treated with GM-CSF. Time to response was 4.1 months for patients assigned to treatment with T-VEC compared to 3.7 months in GM-CSF treated patients. Fifty-four percent of T-VEC responders met the criteria for disease progression before they achieved a response, which means that at least a 25% increase in the lesion size or the development of new lesions was noted even in those patients who went on to achieve a RECIST-specified objective response to T-VEC.

In terms of the secondary endpoints, the overall response rate was significantly better for T-VEC, with 26% of patients achieving an objective response compared with only 6% in the GM-CSF treated group. Eleven percent of the responses to T-VEC were complete responses, compared to only 1 in the GM-CSF group. Numerically, a higher percentage of patients treated with T-VEC had a complete response: 32 patients, or 11% , vs 1, that is less than 1%. Numerically, a higher percentage of patients treated with T-VEC had a partial response: 46 patients, or 15.6%, vs 7 patients, or 5%. The median time to treatment failure was 5.3 months longer in T-VEC treated patients, and the median overall survival was increased by 4.4 months. The median survival was 23 months for T-VEC, and 19 months for GM-CSF, with a *P*-value of 0.05.

Progression-free survival was not reported, but time to treatment failure was reported. This was defined as the time from baseline to the first clinically relevant disease progression for which no objective response was subsequently achieved, or until death. This was 8.2 months for T-VEC patients, vs 2.9 months for those patients assigned to receive GM-CSF.

There were a few additional findings. Patients without lung or visceral metastases and treatment-naïve patients benefited most from T-VEC treatment. That is, the difference in response between T-VEC and GM-CSF patient cohorts were greatest in those subsets than in the overall cohorts.

Regarding the safety of T-VEC, both treatments were tolerable with few discontinuations for adverse events, no treatment-related deaths in either patient cohort, and a low incidence of grade 3 or 4 toxicity. Ten deaths occurred in the T-VEC arm but none were considered treatment-related. Eight of those deaths were considered related to disease progression, 1 was due to sepsis, and 1 was a myocardial infarction with a fatal outcome. In the GM-CSF arm there were 2 deaths related to disease progression. The most common reason for discontinuation of therapy in both treatment arms was progression of disease. Four percent of patients discontinued T-VEC for an adverse event and 2% of patients in the GM-CSF treatment arm discontinued therapy for an adverse event.

Grade 3 or 4 adverse events occurred in 11% of patients treated with T-VEC compared with 5% of patients treated with GM-CSF. The commonest toxicities from T-VEC were chills, fever, injection site pain, nausea, flu-like symptoms, and fatigue. These occurred more often in patients with T-VEC than with GM-CSF.

My thoughts and an assist of this study are summarized as follows: The main point of the study included the achievement of durable local remissions from the injection of this GM-CSF containing oncolytic herpesvirus engineered to optimize the triggering of an enhanced local immune response. The results of the study impact the current state of patient management by demonstrating that durable remissions using this new entity are achievable and that there is a niche for this therapy that has been established and is being further defined by patterns of usage. This is particularly important for patients who are in desperate need of local control that's hard to achieve by other measures such as surgery, radiation therapy, or other forms of systemic therapy. The results of this study impact the future state of patient management because we are already seeing early reports of combination therapy outcomes and ongoing studies that are using cutting-edge combinations of immunotherapies and other forms of systemic therapy in combination with T-VEC to achieve optimal local response and an adjunctive systemic response that may lead to particularly good control of this difficult disease.

Among the questions that remain unanswered include the true abscopal benefit of local injections. How can local therapy responses be turned into benefit at sites that are not injected or injectable? In particular, visceral disease, which is far more likely to lead to the death of patients from this disease than soft tissue and skin metastases that are amenable to injection. We need to learn more about various subtypes of melanoma and their responsiveness to T-VEC. We also need to learn more about which sites of metastatic disease are most likely to respond and how the molecular and immunobiology of the oncolytic herpesviruses, with or without a transgene included in their genome, can be optimized for future therapy of melanoma and other malignant diseases. Thank you.

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Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

Larkin J, et al.

Dr. Kim Margolin

Hello. This is Dr. Kim Margolin, professor in medical oncology at the City of Hope National Medical Center. In this article we will discuss Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The lead study author was James Larkin. In this episode we will discuss Dr. Larkin et al's report of the study of combined nivolumab and ipilimumab for treatment-naïve patients with advanced melanoma, comparing the combination with each of the individual agents. In this trial the progression-free survival for the combination of both of these drugs was compared to the same endpoint for either drug monotherapy in a double-blind phase 3 trial.

The importance of this study was that it provided the first direct comparison of CTLA-4 vs PD-1 blockade alone or in combination. Important aspects of the safety of each regimen, as well as preliminary identification of predictive biomarkers for selection of a therapeutic regimen, were also studied.

The trial design and methodology will now be discussed. Patients enrolled in this trial had previously untreated, unresectable stage III or stage IV melanoma without active brain metastasis. Randomization was balanced between nivolumab monotherapy, combination nivolumab and ipilimumab, or ipilimumab monotherapy, and patients were prestratified based on PD-L1 and *BRAF* V600 status. Nivolumab dosing was 1 mg/kg body weight every 3 weeks x 4 with ipilimumab, then 3 mg/kg every 2 weeks for the combination therapy cohort. Nivolumab dose was 3 mg/kg every 2 weeks for the nivolumab alone cohort, and ipilimumab was 3 mg/kg every 3 weeks x 4 for the ipilimumab alone, as well as for the ipilimumab component of the combination therapy cohort.

All of the regimens were blinded and placebo-controlled with saline infusions. Exclusion factors included active autoimmune disease or brain metastases. Patients must have had a performance status of 0 to 1 and normal organ function. Treatment was continued until disease progression or unacceptable toxicity, but treatment could be continued after progression if patients were believed to have a clinical benefit. The trial endpoints included the co-primary endpoints of progression free survival and overall survival, although only the progression free survival, or PFS, is reported in this paper. The trial also looked at the objective response rate, safety of therapy, and PD-L1 as a potential biomarker.

For the primary endpoint, compared to ipilimumab alone, both nivolumab-containing regimens resulted in longer PFS and a higher objective response rate. For combination therapy, the median PFS was 11.5 months and overall response rate was 58%. For nivolumab alone, median PFS was 6.9 months and the objective response rate was 44%. Compared to ipilimumab, the median progression-free survival was only 3 months and the objective response rate was 19%, similar to prior experience with ipilimumab as a single agent in melanoma.

The *BRAF* mutation status was found not to affect the progression-free survival or the objective response rate in any of the patient cohorts or as a whole. The median progression-free survival for combination treatment was 11.5 months. It was 6.9 months for nivolumab monotherapy and was 2.9 months for ipilimumab monotherapy. The *P*-value was <0.001 for either the nivolumab or combination therapy cohorts vs ipilimumab alone, and that was for the progression-free survival.

Additional findings included the important observation about the PD-L1 status of the tumor. Combination treatment seemed to provide the greatest benefit over single agent therapy in patients whose tumors did not express PD-L1. Combination therapy led to 11.2 months median PFS and an objective response rate of 54% in PD-L1 negative tumors, compared with 5.3 months with monotherapy. For PD-L1 positive tumors, the median PFS was 14 months for nivolumab alone or combination therapy, although there was a numerically greater objective response rate for combination treatment.

Samples were positive on the PD-L1 test if 5% or more of patients had any intensity of staining in an automated immunohistochemical assay that may be used in routine combination with treatment selection in the future should it prove valid in larger future studies. Safety results from the study are extremely important. Adverse events, almost all of which were considered to be immune-related, were more frequent in the combination treatment group, with grade 3 or 4 toxicities in 55% of patients. Thirty-six percent of patients had to discontinue therapy because of an adverse event. Nivolumab monotherapy had the lowest incidence of grade 3 or 4 toxicities and thus the lowest discontinuation rate.

The incidence and severity of adverse events was generally highest in the combination treatment group and it was lowest in the nivolumab monotherapy group. Combination therapy had a higher incidence of grade 3 and 4 toxicities: 55% compared with 16% for nivolumab and 27% for ipilimumab. This was particularly the case for elevation of the ALT: 8% in the combination vs 1% for nivolumab and 1.5% for ipilimumab.

The percent of patients requiring discontinuation of therapy for immune-related adverse events was 7.7% for nivolumab, 36% for combination therapy and 15% for ipilimumab, all of which were statistically significant and clinically quite significant. There were no drug-related deaths in the combination treatment group and there was 1 drug-related death in each of the monotherapy arms of therapy. Selected adverse events of importance include the occurrence of grade 3 to 4 diarrhea which occurred at 2% for the nivolumab-treated patients, 9% for those assigned to combination therapy and 6% for ipilimumab. Colitis, a more severe form of diarrhea that can be dangerous and even life-threatening, occurred at a grade 3 to 4 level in 0.6% of patients on nivolumab, 7.7% of patients assigned to combination therapy and 8.7% of patients receiving ipilimumab.

Increased alanine aminotransferase, as mentioned earlier, was about 1% in nivolumab alone, 8.3% for patients receiving the combination therapy and 1.6% for patients receiving ipilimumab as a single agent.

There were some limitations to this study and caveats in interpretation of the data. The overall survival was not reported in this trial because the trial results were so dramatic that it was most appropriate to report these results as early as could be statistically valid, that is as soon as the progression-free survival endpoint was met with statistical certainty.

Differences in the outcomes based on PD-L1 expression were exploratory and retrospective and it was not a preplanned prospective analysis, therefore validation of this test, especially in the context of differences in the performance of the PD-L1 assays will need to occur in future.

Some of my thoughts about this study and its analysis are as follows: This critically important study of a combination of our currently 2 best immunotherapies for melanoma, and probably for a number of other solid tumors, demonstrated the expected differences favoring combination therapy over ipilimumab and somewhat over nivolumab alone. These results were not unexpected based on prior data for any of these 3 regimens in phase 2 trials. The unexpected finding that the difference between combination therapy and single agent nivolumab outcomes appeared to segregate the patients with PD-L1 non-expressing tumors or the provocative finding that requires follow-up for both survival data as well as more investigation of the underlying mechanism and biology of this important observation. This may relate directly to the mechanisms of action of these 2 immune checkpoint blocking antibodies and help to inform the design of future strategies, both for therapeutic outcomes as well as for reduction of toxicities.

The results of this study have dramatically impacted the current state of patient management and will continue to do so. Despite the fact that the data were reported in preliminary form with the progression-free survival as the primary endpoint and the overall survival still pending longer follow-up, and despite the fact that the data are fraught with a number of caveats and concerns, including in large part the enormous toxicities of the combination regimen and the need for a great deal of experience to safely and effectively manage these patients, they do provide clinicians a benchmark for what to expect both therapeutically and with regard to toxicities. They raise the provocative question of whether PD-L1 is an adequate and reliable biomarker predictive of response and allowing us to decide who needs to have combination therapy with the toxicities and who can get away with single agent PD-1 blocking antibody therapy.

Among the big questions for 2016, and subsequently, include whether to choose single or combination checkpoint blockade, and in patients with an activating *BRAF* mutation in their melanoma, whether the first-line of therapy should be checkpoint blockade such as described here, or combination MAP kinase inhibitor therapy. This question is being addressed in an important randomized study in the US cooperative group's EA6134, which randomizes patients with *BRAF*-mutant melanoma between these 2 therapy approaches as first-line. Within the context of that study is a crossover to the opposite line of therapy for patients who progress, and a number of immunologic and molecular biological correlates will allow for maximum utilization of the ultimate clinical results of this study once it's completed.

Though the results of Dr. Larkin's study also impact the future state of patient management, it's still not clear how to select first-line therapy for advanced melanoma. Most of the current and in-development clinical trials feature single agent, that is the vast majority, or double-immune checkpoint blockade, that is the minority, in combination with another agent to enhance activity, to reduce toxicity, or to treat a patient subset that does not traditionally benefit from other therapies. These include the uveal primaries, which are notoriously quite resistant to immunotherapy, as well as molecularly targeted therapy and cutaneous melanoma metastatic to the brain, which is a difficult complication of this disease and often results in the patient's death.

Among the unanswered questions remaining include the optimization and discovery of predictive factors for selection of first-line therapy with maximum therapeutic index favoring therapeutic outcome and minimum toxicities; how to best manage patient characteristics; which ones should they be; tumor characteristics and interactions among the tumor microenvironment; the tumor and the patient genetics, will all need to be incorporated into the design of future treatment regimens and will benefit in great part from the results of this present study. Thank you.

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4 Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma

Ribas A, et al.

Dr. Kim Margolin

Hello. This is Dr. Kim Margolin, professor in medical oncology at the City of Hope National Medical Center. The title of this article by Dr. Antoni Ribas et al is Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. In this episode we will discuss Dr. Ribas' analysis of patients enrolled in open-label phase 1B trials of pembrolizumab. In this study, Dr. Ribas and his colleagues looked at long-term outcomes using a pooled analysis of patients enrolled in the KEYNOTE-001 trial and considered factors that might affect response to pembrolizumab.

The trial design and methodology are described now. Six hundred fifty-five patients were included in this pooled analysis from the KEYNOTE-001 study. The analysis included patients treated in open-label randomized or nonrandomized cohorts for dose confirmation. These cohorts were comprised of a variety of patients including treatment naïve, ipilimumab-naïve, *BRAF* V600 mutant and wild-type tumors that were then recorded by subset analysis. Objective response rate was the primary endpoint of this retrospective report of pooled studies.

Open-label phase 1B trial with 665 patients randomized or nonrandomized study groups treated with pembrolizumab 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, or 2 mg/kg every 3 weeks, which is the approved dose, until disease progression, intolerable toxicity or a decision on the part of the patient or investigator that it was not any longer in the patient's best interest to continue therapy. The median follow-up of patients included in the pooled analysis was 15 months.

The key findings will now be presented: For the primary endpoint, approximately one-third of patients with advanced melanoma experienced an objective response to pembrolizumab and another approximately 40% of patients experienced some evidence of tumor regression that did not meet criteria for objective response, but the patient may also have benefited from pembrolizumab therapy. The objective response rate across treatment cohorts was 33%, and 12-month progression-free survival was 35% of patients. Overall survival median was 23 months.

There were some differences in these outcomes for different subgroups that would require a prospective study with representative patient numbers. For example, fully treatment-naïve patients with elevated vs normal LDH, patients in the M1B or most unfavorable category of metastatic disease, considerations of the baseline tumor size, and the *BRAF* and other oncogene mutational status. Though the objective response rate was 33% across the board, the 12-month progression-free survival fraction was 35% of patients.

Among the responders, 44% had a response lasting at least 1 year and the median duration of response was 28 months. The median overall survival was 23 months.

The 12-month progression-free survival was 52% of patients and the median survival was 31 months. The response rate in ipilimumab-naïve cohorts of patients vs previously ipilimumab-treated groups was 39% vs 29%. That reflects early practice in the field and the requirements of previous studies.

Antitumor activity was observed across all clinical pathologic factors examined although some baseline clinical features were associated with a better response. For example, baseline tumor size, baseline tumor burden independent of ipilimumab pretreatment, category M1B disease, and treatment-naïve patients, all prognostic factors unlikely to be treatment-specific predictors and all requiring prospective validation in studies where subjects are stratified by these factors or are represented in adequate numbers to assess their contribution to the outcomes.

For *BRAF*-mutant tumors, the overall response rate was a bit lower: 26% vs 36% objective responses in *BRAF* wild-type tumors. However, this may have been due to the fact that many of the patients with a *BRAF* mutation were previously treated with MAP kinase inhibitors. When response based on *BRAF* status was limited to fully treatment-naïve patients, there was little difference in the objective response rate between *BRAF*-mutant and *BRAF* wild-type tumors–that is 50% vs 45% objective response rate. Overall, these pooled results align with those that have been demonstrated from randomized cohorts of patients in subsequent studies.

Grade 3 or 4 toxicities occurred in 14% of patients and they were not affected by previous ipilimumab treatment. Of course, it should be noted that patients who had experienced severe immune-related adverse events from prior ipilimumab treatment were excluded from pembrolizumab studies, and therefore the overall baseline characteristics of this particular pooled patient group is probably somewhat more favorable. Pembrolizumab dosing schedule also did not affect the incidence or severity of grade 3 or 4 toxicities. Adverse events led to the discontinuation of therapy for only 4% of patients.

My thoughts and analysis of this study include some of the following points: This is the first study to evaluate in large patient numbers the dose schedule and important patient and tumor characteristics that contribute to patient and physician expectations for pembrolizumab therapy of advanced melanoma. The results of the study impact the current state of patient management. In particular, this study got the drug approved in the second-line setting, an approval which was followed soon thereafter by an approval of nivolumab, a similar PD-1 blocking fully-human antibody, and subsequently by first-line approvals for both drugs.

Finally, in late 2015, the combination of PD-1 plus CTLA-4 blockade was approved for the therapy of metastatic melanoma. The results of this study also impact the future state of patient management because they set the stage for single-agent therapy as a comparator and contrasting agent for subsequent trials of combinations or other immune checkpoint or other forms of immunotherapy for metastatic melanoma. This drug's results provide the backbone for many investigational therapeutic strategies ranging across a broad spectrum of important combinations. It will provide a control arm single-agent pembrolizumab for many future phase 3 comparisons of new regimens compared with standard therapies.

Among the questions that remain unanswered include the very important study of mechanisms of resistance, both intrinsic—that is explaining why some patients don't respond in the first place—and acquired—which characterizes patients who initially experienced a benefit from pembrolizumab but then relapsed and progressed. The selection of patients and tumors for optimal therapy with this or related agents will be a very important component of future studies as we learn from studies such as this some of the exploratory or hypothesis-generating findings, such as the association of PD-L1 with activity.

Prediction of the rare but important toxicities, as well as the more common immune-related adverse events that are unique to these agents or may be common to immune checkpoint blockade, are also going to be studied in the context of future studies and this particular large pooled analysis provides a good baseline for such studies as well. Thank you.

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